```
FULL ESTIMATED COST                                    0.21       0.21

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FILE LAST UPDATED:         9 AUG 2005      <20050809/UP>
MOST RECENT UPDATE WEEK:       200531        <200531/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

=> s hydroxytamoxifen or (hyrdroxy tamoxifen)
           268 HYDROXYTAMOXIFEN
            13 HYRDROXY
          5058 TAMOXIFEN
            15 TAMOXIFENS
          5061 TAMOXIFEN
                 (TAMOXIFEN OR TAMOXIFENS)
             0 HYRDROXY TAMOXIFEN
                 (HYRDROXY(W)TAMOXIFEN)
L1         268 HYDROXYTAMOXIFEN OR (HYRDROXY TAMOXIFEN)

=> s tamoxifen
          5058 TAMOXIFEN
            15 TAMOXIFENS
L2        5061 TAMOXIFEN
                 (TAMOXIFEN OR TAMOXIFENS)

=> s l2/ab
            67 TAMOXIFEN/AB
             2 TAMOXIFENS/AB
L3          67 (TAMOXIFEN/AB)
                 ((TAMOXIFEN OR TAMOXIFENS)/AB)

=> s l2/ti
L4          25 (TAMOXIFEN/TI)

=> s l4 or l2
L5        5061 L4 OR L2

=> s l4 or l3
L6          70 L4 OR L3

=> s breast or mammar
=> s breast or mammar?
         28618 BREAST
          1130 BREASTS
         28849 BREAST
                 (BREAST OR BREASTS)
         13019 MAMMAR?
L7       34444 BREAST OR MAMMAR?

=> s cancer? or tumor? or neoplas?
         70495 CANCER?
         59135 TUMOR?
         20255 NEOPLAS?
L8       88096 CANCER? OR TUMOR? OR NEOPLAS?

=> s l7/ab
          1789 BREAST/AB
            86 BREASTS/AB
          1818 BREAST/AB
                 ((BREAST OR BREASTS)/AB)
           241 MAMMAR?/AB
L9        2015 (BREAST/AB OR MAMMAR?/AB)
```

```
=> s l9 and l8
L10       1529 L9 AND L8

=> s percutaneous? or topical?
          10644 PERCUTANEOUS?
          49656 TOPICAL?
L11       57173 PERCUTANEOUS? OR TOPICAL?

=> s l11 and l10
L12         498 L11 AND L10

=> d his

     (FILE 'HOME' ENTERED AT 08:51:47 ON 11 AUG 2005)

     FILE 'PCTFULL' ENTERED AT 08:52:01 ON 11 AUG 2005
L1           268 S HYDROXYTAMOXIFEN OR (HYRDROXY TAMOXIFEN)
L2          5061 S TAMOXIFEN
L3            67 S L2/AB
L4            25 S L2/TI
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L7         34444 S BREAST OR MAMMAR?
L8         88096 S CANCER? OR TUMOR? OR NEOPLAS?
L9          2015 S L7/AB
L10         1529 S L9 AND L8
L11        57173 S PERCUTANEOUS? OR TOPICAL?
L12          498 S L11 AND L10

=> s l12 and l6
L13          10 L12 AND L6

=> s l13 and l1
L14           5 L13 AND L1

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        294498 PY>2002
L15           1 L14 NOT PY>2002

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L15    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2001063292 PCTFULL  ED 20020822
TITLE (ENGLISH):         COMPOSITIONS AND METHODS OF USE OF HET, A NOVEL
                         MODULATOR OF ESTROGEN ACTION
TITLE (FRENCH):          COMPOSITIONS ET UTILISATIONS DE HET, UN NOUVEAU
                         MODULATEUR DE L'ACTION OESTROGENIQUE
INVENTOR(S):             OESTERREICH, Steffi;
                         OSBORNE, C., Kent;
                         LEE, Adrian, V.;
                         FUQUA, Suzanne, A.W.
PATENT ASSIGNEE(S):      BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;
                         OESTERREICH, Steffi;
                         OSBORNE, C., Kent;
                         LEE, Adrian, V.;
                         FUQUA, Suzanne, A.W.
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PATENT INFORMATION:
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MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
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SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US6135 A 20010222
PRIORITY INFO.: US 2000-60/184,097 20000222

=> d abs

L15 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN

ABEN Estrogen Receptor; Nuclear Matrix Protein HET/SAF-B; Transcription; Repression; Antiestrogen; Tamoxifen. Disclosed are methods for the detection of tumor cells, in particular human breast cancer cells. Genetic and antibody probes and methods useful in determining the presence of and monitoring tumor cell proliferation are also described. The methods involve determining HET polypeptide expression, mRNA levels or loss of heterozygosity at human chromosomal locus 19p13 as a measure of tumor cell malignancy. These methods are also of use in distinguishing breast cancers that are resistant to estrogen antagonists, such as tamoxifen, from estrogen antagonist sensitive tumors. Also described are procedures for transforming cells with HET gene containing vectors that express HET polypeptide. Such procedures may be of use in converting tamoxifen-resistant tumors into tamoxifen -sensitive tumors.

ABFR Mots-cles : recepteur d'oestrogene ; proteine de matrice nucleaire HET/SAF-B ; transcription, repression; anti-oestrogene; tamoxifene L'invention concerne des procedes de detection de cellules tumorales, en particulier de cellules du cancer du sein humain. Elle concerne en outre des sondes genetiques et des sondes d'anticorps ainsi que des procedes servant a determiner la presence d'une proliferation de cellules tumorales et des surveiller celle-ci. Ces procedes consistent a mesurer l'expression du polypeptide HET, les taux d'ARNm ou la perte du caractere heterozygote dans le locus chromosomique 19p13, afin de determiner le degre de malignite des cellules tumorales. Ces procedes permettent en outre de distinguer les cancers du sein resistants aux antagonistes de l'oestrogene tels que le tamoxifene, des tumeurs sensibles aux antagonistes de l'oestrogene. L'invention concerne en outre des procedures consistant a transformer des cellules avec des vecteurs contenant un gene HET exprimant le polypeptide HET. Ces procedures peuvent etre utiles pour convertir les tumeurs resistantes au tamoxifene en tumeurs sensibles au tamoxifene.

=> d kwic

L15 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2005 Univentio on STN

ABEN Estrogen Receptor; Nuclear Matrix Protein HET/SAF-B; Transcription; Repression; Antiestrogen; Tamoxifen. Disclosed are methods for the detection of tumor cells, in particular human breast cancer cells. Genetic and antibody probes and methods useful in determining the presence of and monitoring tumor cell proliferation are also described. The methods involve determining HET polypeptide expression, mRNA levels or loss of heterozygosity at human chromosomal locus 19p13 as a measure of tumor cell malignancy. These methods are also of use in distinguishing breast cancers that are resistant to estrogen antagonists, such as tamoxifen, from estrogen antagonist sensitive tumors. Also described are procedures for transforming cells with HET gene containing vectors that express HET

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DETD 1.1 Field of the Invention
The present invention relates generally to cancer biology. In particular, it concerns novel methods and compositions for modulating estrogen actions. The present invention further relates to detection, diagnosis and prognosis of breast cancer and the identification of tamoxifen-resistant breast cancers. Another aspect of the present invention relates to gene therapy for altering the phenotype of tumor cells.

More particularly, it concerns use of expression vectors comprising an BET gene to increase the sensitivity of the tumor cell to estrogen antagonists, or to decrease the sensitivity of the tumor cell to estrogen and estrogen agonists.

Hsp27 plays a role in both growth and drug resistance of human breast cancer cells in culture (Oesterreich et aL, 1993). Hsp27 has been found to contribute to increased drug resistance in CHO cells (Lavoie et al., 1993), colon cancer cells (Garrido et aL, 1996), and testis cancer cells (Richards et al., 1996). Elevated hsp27 levels also correlate with increased invasion of human breast cancer cells (Lemieux et al., 1996). Hsp 27 is not an independent prognostic marker for breast cancer (Oesterreich et al., 1996b). However, hsp27 predicts a significantly worse outcome in 10, a subset of ER-positive/untreated breast cancer patients (Oesterreich et aL, 1996b).

Expression of hsp27 is strongly correlated with the expression of ER in breast tumors .(Oesterreich et aI., 1996b). Several groups have tried to decrease the expression of heat shock proteins in order to circumvent drug resistance in tumors. For example, the antiestrogen toremifene (Mahvi et aL, 1996) and the bioflavonoid quercetin (Sliutz et 1 5 aL, 1996) both decrease hsp. . .

Current therapies for breast cancer are targeted, at least in

part, to the estrogen receptor. A group of compounds known as selective estrogen receptor modulators (SERMs) may be used in the prevention and treatment of breast cancer (Minton, 1999). These compounds mediate agonist or antagonist effects of estrogen on the ER.

However, certain breast cancers are antiestrogen resistant, and it is not unusual, for resistance to develop following antiestrogen therapy. A need exists in the art to distinguish those tumors that are sensitive to antiestrogens from those that are resistant. A method of converting antiestrogen-resistant tumors to antiestrogen-sensitive tumors would be of great benefit for treatment of breast cancer.

. . .

THE INVENTION

The present invention resolves a need in the art for a diagnostic method to differentiate between antiestrogen-resistant and antiestrogen-sensitive breast tumors.

Also provided are compositions and methods of use in converting antiestrogen-resistant to antiestrogen-sensitive tumors, by administering expression vectors comprising an BET coding sequence. Specific examples include compositions and methods of use in differentiating antiestrogen-resistant and antiestrogen-sensitive tumors and in converting antiestrogen-resistant to antiestrogen-sensitive tumors.

Specific antiestrogens that are within the context of the invention include the nonsteroidal compounds Tamoxifen, Toremifene, Idoxifene, Droloxifene, TAT-59, Zindoxifene, Trioxifene, and. . . the steroidal antiestrogens ICI 182,780 (FASLODEXTm) and EM Tamoxifen is a particularly well-known estrogen antagonist that exhibits efficacy for treatment of breast cancer. Some of the other nonsteroidal compounds, e.g. TAT-59, are metabolized into an active metabolite of Tamoxifen or are analogues of Tamoxifen, e.g.. . .

. . .

linked to the region encoding said protein, under conditions effective for the uptake and expression of said nucleic acid by said tumor cell, wherein said cell is converted from a phenotype displaying normal steroid hormone receptor activity to one displaying reduced steroid hormone receptor. . .

. . .

Of course, as detailed herein, some of the primary embodiments of the present invention entail the diagnosing and treatment of breast cancer . Exemplary forms of breast cancer that may be diagnosed and/or treated according to the invention include infiltrating duct carcinoma, lobular carcinoma, medullary carcinoma, mucinous carcinoma, tubular carcinoma,. . .

In some embodiments, the invention relates to methods for detecting resistance to antiestrogens in breast cancer cells, comprising: a) obtaining a sample suspected of containing breast cancer cells; b) contacting said sample with an antibody that specifically binds to an BET polypeptide under conditions effective to bind said antibody. . .

. . .

Western blotting, ELISA. Northern blotting, slot blotting, dot blotting and/or DNA chip assay

Alternative embodiments include methods for predicting antiestrogen resistance in breast cancer cells, comprising: a) measuring the amount of BET gene product in a sample containing breast cancer cells; and b) comparing the amount of BET gene product present in said sample with the amount of BET gene product in samples selected from patients with antiestrogen-resistant and antiestrogen-sensitive breast cancers. Exemplary antiestrogens can be selected from the group consisting of Tamoxifen, Torenffene, Idoxifene, Droloxifene, TAT-59, Zindoxifene, Trioxifene, Raloxifene, ICI 182,780 and EM. . .

The invention also relates to method for predicting antiestrogen resistance in breast cancer cells, comprising: a) obtaining a breast cancer cell sample and a normal cell sample from the same individual; b) amplifying chromosomal DNA from said breast cancer and normal cell samples using primers selected to amplify a chromosomal locus comprising the BET gene; and c) comparing the amplification products from said breast cancer and normal cells, wherein loss of heterozygosity (LOH) at said locus indicated by an amplification product present in the normal cell and missing in the breast cancer cell is indicative of antiestrogen resistance in said breast cancer cell.

In a further embodiment, the invention anticipates methods for detecting anti-estrogen resistance in breast cancer cells, comprising: a) obtaining a sample suspected of containing breast cancer cells; b) measuring the amount of BET gene product in said sample,] wherein said BET gen& product is a molecule. . . in the amount of BET gene product in said sample compared with the amount in normal cells indicates anti-estrogen resistance of breast cancer cells.

The invention further encompasses methods of malignant breast cancer diagnosis, comprising determining loss of heterozygosity (LOH) at a chromosomal locus comprising the BET gene, wherein LOH at said locus is indicative of antiestrogen resistance in breast cancer cells. Likewise, the

invention encompasses
methods of determining likelihood of survival for a breast tumor subject, comprising
determining loss of heterozygosity (LOH) at a chromosomal locus comprising the BET
gene in a breast tumor cell sample from said subject, wherein LOH at said locus is
associated with a decreased probability of survival.

The invention further contemplates methods for altering the phenotype of a
breast tumor cell comprising contacting the cell with a nucleic acid comprising (i) a
DNA sequence encoding a BET protein and (ii) a promoter active in said breast tumor
cell, wherein said promoter is operably linked to the region encoding said protein,
under conditions effective for the uptake and expression of said nucleic acid by said
tumor cell. In some exemplary embodiments, the BET protein has the amino acid
sequence of SEQ ID NO:2. For example, the breast tumor cell mày be converted from
a phenotype resistant to antiestrogen to a phenotype sensitive to antiestrogen. In this
case, the antiestrogen may. . .

FIG. 6A and FIG. 611. BET/SAF-B expression is decreased in antiestrogen-resistant xenograft tumors.

FIG. 7 illustrates a human metaphase spread with the BET PI probe fluorescently
labeling both chromosome 19 homologs at 19p13 >p13.3
FIG. 8 shows an LOH analysis at human chromosomal locus 19p13 of breast tumor
specimens. Breast biopsy DNA (normal and tumor) was analyzed using PCRTm based
microsatellite markers corresponding to 19-pter (Genethon, see Gyapay et aL, 1994).

FIG. 9 illustrates HET expression in primary breast cancers. Frozen tumor powder
was homogenized in 5% SDS, and 25]ig protein was resolved on 7.5% PAGE. After
transferring onto nitrocellulose, BET was detected. . .

FIG. 11 shows that transient transfection of antisense BET into 293 cancer cells
causes an increased rate of cell division, as measured by [3 H]-thymidine incorporation
into DNA. Cells were transfected with 0.02, 0.2. . .
. . .
activity, it is meant that the molecule in question has the ability to inhibit cell transformation, or to prevent
metastasis or invasive tumor growth. Other phenotypes that may be regulated by the
normal BET gene product are angiogenesis, cell adhesion, migration, cell-to-cell
signaling, cell growth,. . .

The term tumor suppressor is well-known to those of skill in the art.

Examples of other tumors suppressors are p53, Rb and p16, to

name a few. While
these molecules are structurally distinct, they form a group of
functionally-related
molecules, of which BET is a member. The uses for which these other
tumor
suppressors now are being exploited are equally applicable here.

The inventors have discovered that the gene encoding the BET protein
(the
1 5 HET gene) is a tumor suppressor gene. BET has been mapped
to chromosomal locus
19p13 p13 Using LOH technology, it was found that this locus is lost in
50-60%
of breast cancer patients, which is higher than the LOH
described for any other tumor
suppressor gene described to date (e.g., p53, Rb).

. . .
the entire BET molecule, the present invention also relates to
fragments of the polypeptide that may or may not retain the
tumor suppressing (or
other) activity of BET. Fragments including the N-terminus of the
molecule may be
generated by genetic engineering of translation stop. . .

. . .
Encoding HET
Nucleic acids according to the present invention may encode an entire
BET
gene, a domain of BET that expresses a tumor suppressing
function, or any other
fragment of the BET sequences set forth herein. The nucleic acid may be
derived from
genomic DNA. . .

4 5 Antisense Constructs
In some cases, mutant tumor suppressors may not be
non-functional. Rather,
they may have aberrant functions that cannot be overcome by replacement
gene
therapy, even where the. . .

4 6 Ribozymes
Another approach for addressing the dominant negative mutant
tumor
suppressor is through the use of ribozymes. Although proteins
traditionally have been
used for catalysis of nucleic acids, another class of macromolecules. .
. .

. . .
I (TN 1)
Platelet-Derived Growth Factor
Duchenne Muscular Dystrophy
SV40
ENHA-NCER/PROMOTER
Polyoma,
Retroviruses
PapiRoma, Virus
Hepatitis B Virus
Human Immunodeficiency Virus
Cytomegalovirus
TABLE3
Element Inducer
Mr II Phorbol Ester (TPA)
Heavy metals
MMTV (mouse mammary tumor Glucocorticoids
virus)

P-Interferon poly(rl)X
poly(rc)
Adenovirus 5 E2 Ela
c-jun Phorbol Ester (TPA), H202
Collagenase Phorbol Ester (TPA)
Stromelysin Phorbol Ester (TPA), IOL-1
SV40 Phorbol Ester (TPA)
Murine NIX. . . Interferon, Newcastle Disease Virus
GRP78 Gene A23187
a Macroglobuhn IL-6
Vitnentin Serum
MHC Class I Gene H-2kB Interferon
HSP70 Ela, SV40 Large T Antigen
Proliferin Phorbol Ester-TPA
Tumor Necrosis Factor FMA
Thyroid Stimulating Hormone a Thyroid Hon-none
Gene
Insulin E Box Glucose
Where a cDNA insert is employed, typically one will typically. . .
. .
that a
nucleic acid encoding a BET gene also may be specifically delivered into a cell type
such as lung, epithelial, or tumor cells, by any number of receptor-ligand systems with
or without liposomes. For example, epidermal growth factor (EGF) may be used as
the receptor for mediated delivery of a nucleic acid encoding a gene in many tumor
cells that exhibit upregulation of EGF receptor. Mannose can be used to target the
mannose receptor on liver cells. Also, antibodies to. . .
. .
most widely used means of large scale production of cells and cell products. However, suspension cultured cells have limitations, such as tumorigenic
potential and lower protein production than adherent T-cells.
. .
of the type that was used to provide the somatic
and myeloma cells for the original fusion. The injected animal develops tumors
secreting the specific monoclonal antibody produced by the fused cell hybrid. The
body fluids of the animal, such as serum or ascites. . .

4.4 Diagnosing Cancers Involving HET
The present inventors have determined that alterations in BET are'associated
with breast cancer and may be associated with other malignancies. Therefore, BET
and the corresponding gene may be employed as a diagnostic or prognostic indicator
of cancer. More specifically, point mutations, deletions, insertions, allelic loss, or
regulatory perturbations relating to BET may cause cancer or promote cancer
development, cause or promote tumor progression at a primary site, and/or cause or
promote metastasis. Other phenomena associated with malignancy that may be
affected by BET expression. . .

Another aspect of the present invention concerns distinguishing tamoxifen-
sensitive from tamoxifen-resistant cancers, more particularly

breast cancers.

Tamoxifen resistance is associated with decreased levels of BET gene products in
breast cancer cells. Determination of BET expression levels, by assay of BET mRNA
or protein, may be used to distinguish tumors that are resistant to estrogen antagonists
(such as tamoxifen) from tumors that are sensitive to estrogen antagonists.

Alternatively, LOH assay may be used to identify tumors that have lost an allele of the
BET gene. Such tumors are expected to show a decreased expression of HET gene
product.

. . .
alterations in the expressed product in a
biological sample. In particular, the present invention relates to the diagnosis or
prognosis of breast cancer.

. . .
a patient with a
sufficiently large reference group of normal patients and patients that have BET-
related pathologies, such as malignant breast tumors. In this way, it is possible to
correlate the amount or type of BET detected (for example, mutant or truncated BET
polypeptides) with various clinical states. In particular applications, such as breast
cancers, it is contemplated that different levels of progression of breast cancer may be
identified. In further embodiments, the sensitivity of tumors to estrogen antagonists,
such as tamoxifen, may be determined.

5 The amplified sequences may then be identified and quantitated. The presence of the
BET gene or mutants thereof may be used in the methods disclosed herein to
determine degree of malignancy, cell tumorigenicity, and potential prognosis/diagnosis
of cancers such as breast cancers.

. . .
as ELISA and
Western blotting. This may provide a screen for the presence or absence of
malignancy, as a predictor of future cancer, or to distinguish tamoxifen-resistant from
tamoxifen-sensitive tumors.

. . .
or inhibition or stimulation of cell-to-cell signaling,
growth, metastasis, cell division, cell migration, soft agar colony formation, contact
inhibition, invasiveness, angiogenesis, apoptosis, tumor progression or other malignant
phenotype. Preferred embodiments include assay of cell replication by incorporation of
radiolabeled thymidine or colony formation. A preferred. . .

. . .
the use of various animal models. By
developing or isolating mutant cells lines that fail to express normal BET, one can
generate cancer models in mice that will be predictive of

cancers in humans and other
mammals. These models may employ the orthotopic or systemic
administration of
tumor cells to mimic primary and/or metastatic cancers
. Alternatively, one may induce
cancers in animals by providing agents known to be responsible
for certain events
associated with malignant transformation and/or tumor
progression. Finally,
transgenic animals (discussed below) that lack a wild-type BET may be
utilized as
models for cancer development and treatment.

. . .

any
route that could be utilized for clinical or non-clinical purposes,
including but not
limited to oral, nasal, buccal, rectal, vaginal or topical.
Alternatively, administration
may be by intratracheal instillation, bronchial instillation,
intradermal, subcutaneous,
intramuscular, intraperitoneal or intravenous injection. Specifically
contemplated are
systemic intravenous injection, regional. . .

. . .

a compound in vivo may involve a variety of
different criteria. Such criteria include, but are not limited to,
survival, reduction of
tumor burden or mass, arrest or slowing of tumor
progression, elimination of tumors,
inhibition or prevention of metastasis, increased activity level,
improvement in immune
effector function and improved food intake.

4.6 Methods for Treating HET Related Malignancies

The present invention also contemplates, in another embodiment, the
treatment
of cancer. The types of cancer that may be treated,
according to the present invention,
are limited only by the involvement of BET. By involvement is meant
that, it is not
even a requirement that BET be mutated or abnormal - the overexpression
of this
tumor suppressor may actually overcome other lesions within
the cell. Thus, it is
contemplated that a wide variety of tumors may be treated
using BET therapy.

In many contexts, it is not necessary that the tumor cell be
killed or induced to
undergo normal cell death or apoptosis. Rather, to accomplish a
meaningful
treatment, all that is required is that the tumor growth be
slowed to some degree. It
may be that the tumor growth is completely blocked, however,
or that some tumor
regression is achieved. Clinical terminology such as remission and
reduction of
tumor burden also are contemplated given their normal usage.

In further embodiments, the treatment of cancer with BET
therapy may be
directed towards malignancies. that are or are likely to become
resistant to therapeutic
compounds. In one embodiment, BET therapy may be used to treat
cancer cells that

have become resistant to compounds that inhibit steroid receptors. In another
embodiment, BET therapy may be used to treat cells. . .
. . .
the therapeutic embodiments contemplated by the present inventors is the intervention, at the molecular level, in the events involved in the tumorigenesis of
some cancers. Specifically, the present inventors intend to provide, to a cancer cell, an
expression construct capable of providing BET to that cell. Any of the gene sequence
variants discussed above which would encode. . .

Various routes are contemplated for various tumor types. The section below
on routes contains an extensive list of possible routes. For practically any tumor,
systemic delivery is contemplated. This will prove especially important for attacking
microscopic or metastatic cancer. Where discrete tumor mass may be identified, a
variety of direct, local and regional approaches may be taken. For example, the tumor
may be injected directly with the expression vector. A tumor bed may be treated prior
to, during or after resection. Following resection, one generally will deliver the vector
by a catheter left in place following surgery. One may utilize the tumor vasculature to
introduce the vector into the tumor by injecting a supporting vein or artery. A more
distal blood supply route also may be utilized.
. . .
different embodiment, ex vivo gene therapy is contemplated. This approach is particularly suited, although not limited, to treatment of bone marrow
associated cancers. In an ex vivo embodiment, cells fromthe patient are removed and
maintained outside the body for at least some period of time. During this period, a
therapy is delivered, after which the cells are reintroduced into the patient. Preferably,
any tumor cells in the sample have been killed.
. . .
own bone marrow donor. Thus, a normally lethal dose of irradiation or chemotherapeutic may be delivered to the patient to HI tumor cells, and the bone
marrow repopulated with the patient's own cells that have been maintained (and
perhaps expanded) ex vivo. Because bone marrow is often contaminated with tumor
cells, it is desirable to purge the bone marrow of these cells. Use of gene therapy to
accomplish this goal is yet. . .

4 2 Immunotherapies
Immunotherapeutics, generally, rely on the use of immune effector cells and
molecules to target and destroy cancer cells. The immune effector may be, for
example, an antibody specific for some marker on the surface of a tumor cell. The
antibody alone may serve as an effector of therapy or it may recruit other cells to
actually effect cell killing.. . . targeting agent. Alternatively,

the effector may be a lymphocyte
carrying a surface molecule that interacts, either directly or
indirectly, with a tumor cell
target. Various effector cells include cytotoxic T cells and NK cells.
. . .
part of a
combined therapy, in conjunction with BET-targeted gene therapy. The
general
approach for combined therapy is discussed below. Generally, the
tumor cell must
bear some marker that is amenable to targeting, i.e., is not present on
the majority of
other cells. Many tumor markers exist and any of these may be
suitable for targeting in
the context of the present invention. Common tumor markers
include
carcinoembryonic antigen, prostate specific antigen, urinary
tumor associated antigen,
fetal antigen, tyrosinase (p97), gp68, TAG-72, MUG, sialyl Lewis
antigen, MucA,,
MucB, PLAP, estrogen receptor, larninin receptor, erb B and. . .

4 3 Combined Therapy with Immunotherapy, Traditional Chemo- or
Radiotherapy
1 5 Tumor cell resistance to DNA damaging agents represents a
major problem in
clinical oncology. One goal of current cancer research is to
find ways to improve the
efficacy of cherno- and radiotherapy. One way is by combining such
traditional therapies
with gene therapy. For example, the herpes simplex-thyraidine kinase
(HS-tk) gene, when
delivered to brain tumors by a retroviral vector system,
successfully induced susceptibility
to the antiviral agent ganciclovir (Culver et al., 1992). In the context
of. . .

To HI cells, inhibit cell growth, inhibit metastasis, inhibit
angiogenesis or otherwise
reverse or reduce the malignant phenotype of tumor cells,
using the methods and
compositions of the present invention, one would generally contact a
target cell with an
BET expression construct. . .

I In treating cancer according to the invention, one would
contact the tumor cells
withan agent in addition to the expression construct. This may be
achieved by irradiating
<------User Break------>

UV-light, y-rays or even
I 0 microwaves. Alternatively, the tumor cells may be
contacted with the agent by
administering to the subject a therapeutically effective amount of a
pharmaceutical
composition comprising a. . .

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L1 268 S HYDROXYTAMOXIFEN OR (HYRDROXY TAMOXIFEN)
L2 5061 S TAMOXIFEN

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L4            25 S L2/TI
L5          5061 S L4 OR L2
L6            70 S L4 OR L3
L7         34444 S BREAST OR MAMMAR?
L8         88096 S CANCER? OR TUMOR? OR NEOPLAS?
L9          2015 S L7/AB
L10         1529 S L9 AND L8
L11        57173 S PERCUTANEOUS? OR TOPICAL?
L12          498 S L11 AND L10
L13           10 S L12 AND L6
L14            5 S L13 AND L1
L15            1 S L14 NOT PY>2002

=> s l14 not py>2003
        184564 PY>2003
L16            2 L14 NOT PY>2003

=> d ibib 1

L16    ANSWER 1 OF 2     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2003039466 PCTFULL  ED 20030520  EW 200320
TITLE (ENGLISH):         METHOD OF TREATING OESTROGEN RESPONSIVE BREAST
                         CANCER
TITLE (FRENCH):          METHODE DE TRAITEMENT DU CANCER DU SEIN
                         REPONDANT AUX OESTROGENES
INVENTOR(S):             WONG, Grace, 100 Arlington Road, Brookline, MA 02467,
                         US [CN, US];
                         ESHKOL, Aliza, Ch. Du Petit Molard 1, CH-Ch-1278 La
                         Rippe, CH [IL, CH];
                         DELUCA, Giampiero, Chemin de la Florence 15, CH-1208
                         Geneva, CH [IT, CH]
PATENT ASSIGNEE(S):      APPLIED RESEARCH SYSTEMS ARS HOLDING N.V., Pietermaai
                         15, Curacao, AN [NL, NL], for all designates States
                         except US;
                         WONG, Grace, 100 Arlington Road, Brookline, MA 02467,
                         US [CN, US], for US only;
                         ESHKOL, Aliza, Ch. Du Petit Molard 1, CH-Ch-1278 La
                         Rippe, CH [IL, CH], for US only;
                         DELUCA, Giampiero, Chemin de la Florence 15, CH-1208
                         Geneva, CH [IT, CH], for US only
AGENT:                   EISENSTEIN, Ronald, I.$, Nixon Peabody LLP, 101 Federal
                         Street, Boston, MA 02110$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2003039466         A2 20030515
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                         CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                         IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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       RW (ARIPO):       GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
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                         NL PT SE SK TR
       RW (OAPI):        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2002-US35438       A  20021105
PRIORITY INFO.:          US 2001-60/332,939       20011106
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=> d ibib l14 1

L14    ANSWER 1 OF 5     PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2005058297 PCTFULL  ED 20050706  EW 200526
TITLE (ENGLISH):         USE OF 4-HYDROXYTAMOXIFEN FOR THE PREPARATION
                         OF A MEDICAMENT FOR THE TREATMENT OF GYNECOMASTIA
TITLE (FRENCH):          UTILISATION DE 4-HYDROXYTAMOXIFENE DANS LA PREPARATION
                         D'UN MEDICAMENT DESTINE AU TRAITEMENT DE LA
                         GYNECOMASTIE
INVENTOR(S):             LE NESTOUR, Elisabeth, 6, rue de Chaufourmiers, F-75019
                         Paris, FR [FR, FR];
                         PALUMBO, Andrew, R., 7505 Colonial Road, Brooklyn, NY
                         11209-2905, US [US, US]
PATENT ASSIGNEE(S):      LABORATOIRES BESINS INTERNATIONAL, 5, rue du Bourg
                         l'Abbe, F-75003 Paris, FR [FR, FR], for all designates
                         States except US;
                         LE NESTOUR, Elisabeth, 6, rue de Chaufourmiers, F-75019
                         Paris, FR [FR, FR], for US only;
                         PALUMBO, Andrew, R., 7505 Colonial Road, Brooklyn, NY
                         11209-2905, US [US, US], for US only
AGENT:                   NARGOLWALLA, Cyra$, Cabinet Plasseraud, 65/67, rue de
                         la Victoire, F-75440 Paris Cedex 09$, FR
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:

                         NUMBER              KIND     DATE
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                         WO 2005058297         A1 20050630
DESIGNATED STATES
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                         RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
                         VC VN YU ZA ZM ZW
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       RW (EAPO):        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):         AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT
                         LT LU MC NL PL PT RO SE SI SK TR
       RW (OAPI):        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2004-EP14295       A  20041213
PRIORITY INFO.:          EP 2003-03293156.0       20031215
                         US 2003-10/734,640       20031215


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     (FILE 'HOME' ENTERED AT 08:51:47 ON 11 AUG 2005)

     FILE 'PCTFULL' ENTERED AT 08:52:01 ON 11 AUG 2005
L1           268 S HYDROXYTAMOXIFEN OR (HYRDROXY TAMOXIFEN)
L2          5061 S TAMOXIFEN
L3            67 S L2/AB
L4            25 S L2/TI
L5          5061 S L4 OR L2
L6            70 S L4 OR L3
L7         34444 S BREAST OR MAMMAR?
L8         88096 S CANCER? OR TUMOR? OR NEOPLAS?
L9          2015 S L7/AB
L10         1529 S L9 AND L8
L11        57173 S PERCUTANEOUS? OR TOPICAL?
L12          498 S L11 AND L10
L13           10 S L12 AND L6
L14            5 S L13 AND L1
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L15             1 S L14 NOT PY>2002
L16             2 S L14 NOT PY>2003

=> s l2 and l2
L17          5061 L2 AND L2

=> s l17 and l12
L18           145 L17 AND L12

=> s l2/clm
L19           752 (TAMOXIFEN/CLM)

=> s l1/clm
              29 HYDROXYTAMOXIFEN/CLM
               3 HYRDROXY/CLM
             752 TAMOXIFEN/CLM
               0 HYRDROXY TAMOXIFEN/CLM
                   ((HYRDROXY(W)TAMOXIFEN)/CLM)
L20           29 (HYDROXYTAMOXIFEN/CLM OR (HYRDROXY TAMOXIFEN/CLM))

=> s l20 or l19
L21           757 L20 OR L19

=> s l21 and l18
L22            36 L21 AND L18

=> s l22 not py>2002
          294498 PY>2002
L23            16 L22 NOT PY>2002

=> s l23 not py>2001
          398484 PY>2001
L24            15 L23 NOT PY>2001

=> d ibib 5

L24    ANSWER 5 OF 15    PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:        2001054699 PCTFULL  ED 20020827
TITLE (ENGLISH):         SELECTIVE ESTROGEN RECEPTOR MODULATORS IN COMBINATION
                         WITH ESTROGENS
TITLE (FRENCH):          MODULATEURS SELECTIFS DU RECEPTEUR D'OESTROGENE, EN
                         COMBINAISON AVEC DES OESTROGENES
INVENTOR(S):             LABRIE, Fernand
PATENT ASSIGNEE(S):      ENDORECHERCHE, INC.;
                         LABRIE, Fernand
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2001054699         A1 20010802
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                         CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
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                         MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                         TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
                         SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
                         DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
                         CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2001-CA86          A  20010126
PRIORITY INFO.:          US 2000-60/178,601       20000128

=> d scan
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L24     15 ANSWERS    PCTFULL   COPYRIGHT 2005 Univentio on STN
TIEN    METHOD OF TREATMENT OF PROSTATE CANCER
TIFR    METHODE DE TRAITEMENT DU CANCER DE LA PROSTATE

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):2

L24     15 ANSWERS    PCTFULL   COPYRIGHT 2005 Univentio on STN
TIEN    METHODS FOR IDENTIFYING, TREATING OR MONITORING ASYMPTOMATIC PATIENTS
        FOR RISK REDUCTION OR THERAPEUTIC TREATMENT OF BREAST CANCER
TIFR    PROCEDES D'IDENTIFICATION, DE TRAITEMENT OU DE CONTROLE DES PATIENTS
        ASYMPTOMATIQUES, POUR LA REDUCTION DES RISQUES OU LE TRAITEMENT
        THERAPEUTIQUE DU CANCER DU SEIN

L24     15 ANSWERS    PCTFULL   COPYRIGHT 2005 Univentio on STN
TIEN    BCMP-7 AS MARKER FOR DIAGNOSIS OF BREAST CANCER
TIFR    BCMP 7 EN TANT QUE MARQUEUR POUR LE DIAGNOSTIC DU CANCER DU
        SEIN

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> d his

     (FILE 'HOME' ENTERED AT 08:51:47 ON 11 AUG 2005)

     FILE 'PCTFULL' ENTERED AT 08:52:01 ON 11 AUG 2005
L1          268 S HYDROXYTAMOXIFEN OR (HYRDROXY TAMOXIFEN)
L2         5061 S TAMOXIFEN
L3           67 S L2/AB
L4           25 S L2/TI
L5         5061 S L4 OR L2
L6           70 S L4 OR L3
L7        34444 S BREAST OR MAMMAR?
L8        88096 S CANCER? OR TUMOR? OR NEOPLAS?
L9         2015 S L7/AB
L10        1529 S L9 AND L8
L11       57173 S PERCUTANEOUS? OR TOPICAL?
L12         498 S L11 AND L10
L13          10 S L12 AND L6
L14           5 S L13 AND L1
L15           1 S L14 NOT PY>2002
L16           2 S L14 NOT PY>2003
L17        5061 S L2 AND L2
L18         145 S L17 AND L12
L19         752 S L2/CLM
L20          29 S L1/CLM
L21         757 S L20 OR L19
L22          36 S L21 AND L18
L23          16 S L22 NOT PY>2002
L24          15 S L23 NOT PY>2001

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---Logging off of STN---


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Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                           21.54      21.75
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STN INTERNATIONAL LOGOFF AT 09:00:36 ON 11 AUG 2005